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Re: Federal Register: December 4, 2000 (Vol. 65, No. 233), pages 75727-75730: substances nominated by the National Toxicology Program (NTP) for toxicology studies: All-trans-Retinyl palmitate (CASRN 79-81-2)

Dear Sirs,

In the Federal Register December 4, 2000 (Vol. 65, No. 233) all-trans-retinyl palmitate was nominated by the Food and Drug Administration for phototoxicity and photocarcinogenicity testing. The rationale for its nomination was described as follows: *widespread use in cosmetic products, known biochemical and histological alterations; other retinoids known to enhance photocarcinogenicity.* Details of the rationale for the nomination of retinyl palmitate were described in a document "All-Trans-Retinyl Palmitate, October 2000" issued by the Center for Food Safety and Applied Nutrition of the Food and Drug Administration (FDA CFSAN).
We wish to comment on this nomination as follows:

1) Use of All-trans-Retinyl Palmitate in Drugs (Item No 4.0 of the CFSAN document)

The CFSAN document mentions on page 10 that over the counter and prescription drugs containing retinyl palmitate have been approved by the Food and Drug Administration in 1994 and 1999.
Given that topical drugs containing all-trans-retinyl palmitate were approved for human use, it is reasonable to assume that the photosafety of these drugs has been evaluated

by CDER. Thus the substance was found not to pose a significant risk of enhancing photocarcinogenicity, or, alternatively, its potential risk could be adequately addressed by a warning on a package insert.
If the evidence for photo-safety of these drugs were deemed adequate, there would be no need for further testing of cosmetic use of all-trans-retinyl palmitate. On the other hand, if a potential risk could be addressed by an appropriate warning on a package insert, we believe that a similar approach may be taken for cosmetics contain retinyl palmitate.
For example, a sun warning label on the package may adequately safeguard consumer safety without conducting the proposed photocarcinogenicity study.

2) Relevance of the Proposed Photocarcinogenicity Study on All-trans-retinol for the Assessment of Human Risk (Summary and item 7.2 of the CFSAN document):

At the end of the summary of the CFSAN document the rationale for animal testing is described as follows: "Experimental studies have indicated that topically applied retinoic acid can, under some conditions of testing, enhance photocarcinogenesis."
This statement acknowledges the well-known results that test conditions may determine the outcome of photocarcinogenicity testing of retinoids. The CFSAN review of previous photocarcinogenicity studies on retinoids such as all-trans retinoic acid (see: 7.2 Photocarcinogenesis) describes some studies which supported possible photo-co-carcinogenic effects of retinoids, whereas other studies reported a reduced UV-mediated tumor onset and/or incidence.
The CFSAN review acknowledges "that our current knowledge of the effects of retinoic acid on photocarcinogenesis may not allow a mechanistic explanation for the differences in outcome for studies...." This uncertainty is confirmed by the precautions for the use of dermal drugs containing all-trans retinoic acid, which describe positive as well as negative results of photo(co)carcinogenicity tests (Physician's Desk Reference, 2000).

On the other hand, the standard photo(co)carcinogenicity test in the hairless mouse is performed with the objective to obtain a classification of a substance as potentially "photo(co)carcinogenic" or "non-photo(co)carcinogenic".
However, retinoids such as all-trans-retinoic acid has yielded positive as well as negative results, depending on test conditions. Given that the test parameters which may be responsible for the contradicting results are largely unknown and taking into account that all-trans-retinyl palmitate is closely related to all-trans retinoic acid, it may be reasonably expected that the same uncertainty will apply to the projected test with all-trans-retinyl palmitate. CFSAN acknowledges this dilemma as follows: "Similarities between the biochemical and histological effects of topically applied retinyl palmitate and retinoic acid on skin suggest that these (photocarcinogenicity) studies are relevant for assessing the need for testing the effects of retinyl palmitate on photocarcinogenesis" (Item 7.2 Photocarcinogenesis).
Conflicting results of previous photo(co)carcinogenicity studies on all-trans retinoic may predict further conflicting results of the proposed tests on all-trans-retinyl palmitate. Thus the objection may be raised whether it is reasonable to perform a test which is likely to yield positive (or negative) results of unknown relevance to a human health risk.

3) Mechanistic Studies in Animal to Assess the Phototoxic and/or Photo(co)carcinogenic Potential of All-trans-Retinyl Palmitate (Item 8.0 – Requested Studies):

The CFSAN document describes numerous animal studies on the photo-toxic and/or photocarcinogenic potential of retinoids and concludes that additional animal studies are required.
However, we noted a complete absence of references to relevant human studies evaluating the effect of these materials on sun sensitivity in human skin. Not a single human study on the effect of retinoids in humans is presented in the rationale for testing. Given that the objective of the NTP program is the evaluation of potential health risk to humans, we feel that clinical studies on relevant endpoints in humans should be given preference over animal tests.
In addition, human data may clarify the relevance of the findings of those animal studies already conducted and would be a more appropriate use of NTP and CFSAN resources than additional animal studies.
Item 8.0 (Requested Studies) states that "A study of the photocarcinogenesis of retinyl palmitate, under conditions relevant to the use of retinyl palmitate in cosmetics is requested. Additional mechanistic studies are needed to establish the relevance of the results obtained in the selected animal model"
This statement acknowledges again that the relevance of the hairless mouse model is unknown. Here the question may be raised whether it is reasonable to perform safety testing in an animal model of unknown relevance at all. In our view, it appears more reasonable to establish the relevance of the animal model, prior to performing a safety test of unknown relevance.
In addition, further "mechanistic studies" are proposed in animal models and in the skin of the experimental (animal) model". In our view, the most relevant question concerning the safe use of cosmetics is their effect on human skin, and not on their effect in experimental animal models of uncertain relevance. We believe that an evaluation of the relevance of data from existing photocarcinogenicity studies would be a more reasonable approach. Key safety questions may be the following:

- Do the test materials that were positive for photo(co)carcinogenicity in the experimental animal model increase the sun sensitivity of human skin?
- What is the effect of materials that were negative for photo(co)carcinogenicity in the experimental animal model on sun sensitivity of human skin?

This basic information may provide more insight into the risk of enhancement of ultraviolet-induced skin cancer than yet another animal study.

5) General Comment on the Status of Phototoxicity / Photo(co)carcinogenicity Testing on Drugs and Cosmetic Ingredients:

Actions taken by FDA CFSAN and CDER during the last two years and the establishment of the photocarcinogenicity testing facility at the National Center for Toxicology Research have highlighted recent concerns about the potential photo(co)carcinogenicity of drugs and certain cosmetic ingredients.
However, it is difficult to understand why additional photocarcinogenicity studies are being initiated by FDA-CFSAN before FDA-CDER addresses the comments submitted in response to the draft guidelines for photosafety testing of drugs (published in January 2000). Comments by the Pharmaceutical Research and Manufacturers of America and

the Cosmetic Toiletry and Fragrance Association may be specifically relevant to the present proposal to test retinyl palmitate. Key comments included the following:

- With the exception of 8-MOP, no clear example exists of a human photo-carcinogen.
- The photogenotoxic activity of 8-MOP may easily be measured in short-term in vitro tests
- Human and rodent skin differ in their capacity to repair UV-induced damage and their antioxidant capacity
- The epidermis of the SKH1 (hr/hr) albino mouse is only 1 to 2 cell layers thick and lacks pigmentation
- The percutaneous penetration of topically applied substances in mice are greater than that in human
- there is lack of understanding of the possible mechanisms of indirect enhancement of UV induced tumors

In summary, these comments raised the issue of absence of adequate validation of the rodent photo(co)carcinogenicity test and the considerable uncertainty about its relevance to human safety.
Finally, under the CDER proposed guidelines for photosafety testing of drugs, manufacturers have been given an option of strengthening warning labels in lieu of conducting photocarcinogenicity assays.

It would seem appropriate for CFSAN to take the same approach for all-trans-retinyl palmitate. Such a mandatory warning labelling of cosmetics containing alpha-hydroxy acids has been proposed in a citizen petition of CTFA. However, a response of CFSAN to this proposal is still outstanding.

6) Conclusion:

In summary, we believe that long-term photosafety tests should be conducted only when they can provide useful information. The proposed study of retinyl palmitate does not meet this criteria. Available resources should be used to investigate the proposed mechanisms for photocarcinogenicity enhancement, in order to evaluate the relevance of the mouse model in man, and to develop alternative methods to evaluate the effect of topical products on sensitivity of human skin to sunlight. Mandatory warning labelling may be a more reasonable and cost-effective approach in lieu of conducting photo(co)carcinogenicity assays.

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